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Authors
Maras, Pamela M
Baram, Tallie Z

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Sculpting the Hippocampus from within: Stress, Spines, and CRH

Pamela M. Maras and **Tallie Z. Baram**
Departments of Anatomy/Neurobiology, Pediatrics and Neurology, UC-Irvine, Irvine, CA, 92697 USA

Abstract

Learning and memory processes carried out within the hippocampus are influenced by stress in a complex manner, and the mechanisms by which stress modulates the physiology of the hippocampus are not fully understood. This review addresses how production and release of the neuropeptide corticotropin-releasing hormone (CRH) within the hippocampus during stress influences neuronal structure and hippocampal function. CRH functions in the contexts of acute and chronic stresses taking place during development, adulthood and aging. Current challenges are to uncover how the dynamic actions of CRH integrate with the well-established roles of adrenal-derived steroid stress hormones to shape the cognitive functions of the hippocampus in response to stress

Keywords

Stress; hippocampus; synapses; glucocorticoids; CRH; cognition

Why study the effects of stress on the hippocampus?

The hippocampal formation is a complex and highly organized brain structure [1] involved in encoding, storing and retrieving information, i.e., in learning and memory [2,3]. Afferent inputs into the hippocampus provide information from both within and outside of the brain, and this information is parsed and processed through specific molecular, functional and structural synaptic mechanisms [4]. Given that these incoming signals convey messages about a changing and evolving environment, it is teleologically reasonable for the hippocampus to be endowed with mechanisms to recognize the salience of incoming new messages and distinguish critical signals from trivial ones. Of specific, paramount importance is the ability to identify, store and react to potentially life-threatening signals.

Stress is an external or internal signal indicating potential or perceived threat [5–8]. Stress is ubiquitous and is biologically important because it enables both rapid and delayed adaptive processes to a changing environment [5–7]. Indeed, the mammalian brain is equipped with numerous sensing devices to identify stress, as well as mechanisms to respond to--and be influenced by--stressful signals [6,9]. The hippocampus appears to be particularly vulnerable

Corresponding author: Baram, T. Z. (tallie@uci.edu), Address: Med Sci I, ZOT 4475, University of California-Irvine, Irvine, California 92697-4475, USA. Tel.: +1-949-824-1063; fax: +1-949-824-1106.

to the effects of stress [6,9–11], although the relationship between stress and hippocampal function is complex, depending on the context and nature of the stress [6,7,12,13]. Mild or short-lasting stress often enhances hippocampal function by augmenting synaptic plasticity, perhaps reflecting the adaptive importance of remembering threatening or dangerous circumstances [6,7,14]. However, these same mechanisms, when activated intensely or for a prolonged period, may render the hippocampus susceptible to detrimental effects of chronic or severe stress [7,14,15]. In fact, chronic stress impairs learning and memory function in both humans and experimental animals [7,10,12–15].

Structural foundations of the actions of stress on hippocampal functions

Stress impacts learning and memory processes, at least in part, through altering the structure of hippocampal neurons [11,15]. These stress-induced changes take place at several levels, ranging from rapid modifications of the synaptic machinery to the eventual restructuring (remodeling) of dendritic branches [9–11]. Indeed, one of the most consistently observed effects of chronic stress on the hippocampus is a reduction (retraction) in the branching of pyramidal cell dendrites [11,16–18]. Dendritic integrity is governed by the presence of functional excitatory synapses, which are located primarily on specialized structures known as dendritic spines [19–21]. Rapid, stress-induced dendritic spine loss has been found in the distribution of eventual dendritic atrophy in adult hippocampus [22–24], suggesting that they are related. Importantly, the number and shape of synapse-bearing spines are dynamic [19–21] and are regulated by factors including neurotransmitters, growth factors and hormones that, in turn, are governed by environmental signals, including stress [25,26]. Thus, a derangement of spine dynamics may provide a mechanism for stress-evoked changes in synaptic function, followed by dendritic loss and cognitive impairments.

Multiple stress mediators shape the hippocampus

Because of the significant impact of stress on hippocampal structure and function, the mechanisms by which stress exerts these effects have been intensely studied [6,7,10]. Multiple mediators regulate the effects of stress on hippocampus (Box 1), and these molecules influence the brain along a continuum of spatial and temporal domains (Figure 1). Glucocorticoids, which are released peripherally in response to stress, can have broad impacts on brain function [5,8,9,27–30], whereas the local release of neurotransmitters and neuropeptides within the hippocampus itself provides for more spatially restricted modulation of specific synaptic populations [6,14]. The repertoire of stress mediators also enables temporal specificity in the regulation of hippocampal neurons [6,14]. Although rapid actions of glucocorticoids have been uncovered [31,32], the receptors of these stress hormones primarily act as transcriptional regulators [30], thereby modulating neuronal function within the timeframe of hours to weeks. In contrast, neurotransmitters and neuropeptides, rapidly released within the hippocampus [6,14], can impact synaptic function and spine dynamics within the timeframe of milliseconds to minutes [6,14]. Working in concert, these diverse signaling pathways provide for the modulation of hippocampal neurons both temporally and spatially, and allow for the fine-tuning of learning and memory processes in response to ever changing environmental conditions [6].

This review focuses on the increasingly recognized contributions of the neuropeptide, corticotropin-releasing hormone (CRH; also known as corticotrophin-releasing factor, CRF), to the structural and functional effects of stress on the hippocampus. The canonical role of CRH is to initiate the neurohormonal response to stress, via its release from cell bodies within the hypothalamic paraventricular nucleus [33]. CRH-expressing neurons are also found in several discrete brain regions, where they contribute to many of the neural and behavioral effects of stress [33,34]. Synthesis and release of CRH within the hippocampus

itself is now established [35–37], and this review discusses the function of hippocampal CRH in mediating the effects of stresses on the function and structure of hippocampal synapses, dendritic spines and neurons throughout development and adulthood.

The architecture and operation of the hippocampal CRH system

A substantial population of CRH-producing cells exists within the pyramidal cell layer of the adult hippocampus [35,36,38,39]. Co-localization studies demonstrate that CRH-producing cells within the mature hippocampus are primarily basket- and chandelier-type interneurons, whose axons form perisomatic and axo-axonic synapses on pyramidal cells, respectively [35,36,39] (Figure 2). Although these interneurons synthesize and release the inhibitory neurotransmitter GABA, the physiological actions of CRH in the hippocampus are generally excitatory [40,41]; CRH applied to hippocampal slices increases the firing rates of pyramidal cells via a shortening of the after-hyperpolarization, and in the presence of an excitatory stimulus, essentially “amplifies” this input [41]. Notably, during development, the numbers of CRH-expressing interneurons are particularly high, and these neurons are accompanied by a transient population of CRH-expressing Cajal-Retzius-like cells, suggesting a role for the peptide in hippocampal maturation [35].

CRH exerts its effects via two receptors: CRH receptor type 1 ($CRHR_1$) and type 2 ($CRHR_2$), which belong to the superfamily of G-protein coupled receptors [42]. $CRHR_1$ and $CRHR_2$ differ in their distribution [37,43,44], as well as their role in mediating behavioral and endocrine responses to stress [45,46]. Pharmacological and physiological data indicate that $CRHR_1$ is primarily responsible for mediating the synaptic actions of this peptide on hippocampal pyramidal cells [47,48]. $CRHR_1$ expression is abundant in pyramidal cells [36,37,44,49], where $CRHR_2$ expression is limited [37,44]. $CRHR_1$ is found not only on the somata [37], but also at asymmetric (excitatory) post-synaptic densities on dendritic spines [36,50], consistent with an interaction of CRH with excitatory hippocampal neurotransmission [49]. The importance of CRH-$CRHR_1$ signaling in the stress-induced activation of hippocampal neurons has been demonstrated: short, physical/psychological stress activates $CRHR_1$-containing pyramidal cells (as indicated by increases in immediate early gene expression), and selective blockade of $CRHR_1$ prior to the stress prevents this activation [36,51]. Furthermore, knockout studies suggest that $CRHR_1$ signaling is required for hippocampal plasticity even in the absence of stress: synaptic potentiation is deficient in hippocampal slices from mice lacking $CRHR_1$ [47], and these mice have learning deficits [52].

Although a role for CRH-$CRHR_1$ signaling in the response of pyramidal neurons to stress is thus apparent, the source of the peptide is not completely resolved. Theoretically, CRH could arrive at hippocampal synapses from other brain regions [53], such as the amygdala [54], where it is released during stress. However, as mentioned above, CRH is synthesized within a substantial population of hippocampal interneurons, and electron microscopy studies have demonstrated that CRH is stored within releasable vesicle pools at axon terminals of these neurons, suggesting local release of endogenous hippocampal CRH [35,36]. In addition, pharmacological and genetic evidence support a role for endogenous hippocampal CRH in sculpting the hippocampus (Box 2).

The effects of CRH on hippocampal structure and function are dose- and time-dependent

CRH (both endogenous peptide released during stress, as well as exogenous peptide applied *in vivo* and *in vitro)*, has dose- and time-dependent effects on mature hippocampus, illustrating the complex relationship between stress and hippocampal function. In particular,

the duration of the stress crucially influences its consequences on learning and memory processes [6,7,12,14]. Stress (and CRH application) lasting minutes results in structural and functional consequences that differ significantly from those of stress lasting for hours, though both of these time-frames might be considered acute [6,12]. Chronic stress, lasting days and weeks, exerts still more distinctive changes in hippocampal physiology and structure [7,10,14–16] (Table 1).

During minutes-long stress, CRH release potentiates synaptic plasticity [55,56] and primes long-term potentiation (LTP) [57,58], a cellular process generally believed to underlie learning and memory [59,60]. The facilitating role of CRH on hippocampal function is further apparent from studies showing improved acquisition and retention in several hippocampus-dependent tasks upon administration of CRH into the brain[57,58,61–64]. The mechanisms by which CRH influences synaptic function and memory at the seconds-to-minutes time window are not fully clarified, but may involve increased presynaptic glutamate release [41] and/or enhanced postsynaptic excitability [49], at least in part via reduction of after-hyperpolarization [40,41], likely through suppression of slow Ca^{2+}-activated K^+ currents [65].

In contrast to the above, the functional effects of stress and CRH exposure lasting roughly an hour or longer transition into reduced synaptic function and plasticity and impairments of learning and memory [10,14]. Within hippocampus, structural changes after hours-long stress include a loss of dendritic spines within the apical dendrites of CA1 and CA3 pyramidal neurons [23,24,50]. The loss of spines within stratum radiatum depends on $CRHR_1$ signaling [22,50], although additional stress-induced spine loss might involve signaling by other stress mediators [23,66,67]. CRH application in nanomolar concentrations (to resemble physiological stress-levels, see Box 2) onto hippocampal organotypic slice cultures recapitulates spine loss in a pattern similar to that provoked by stressful events [22], further supporting a role of CRH-$CRHR_1$ signaling in mediating the cellular effects of stress in the hippocampus. This CRH-mediated selective spine loss, resulting in a net loss of excitatory synapses, is functionally important because it is associated with attenuated LTP selectively within the affected synapses, and with memory defects [50].

When stress extends over days and weeks (ie. chronic stress), it is associated with additional structural changes in hippocampal neurons, including lower total dendritic length and complexity [15–18]. CRH signaling likely contributes to these changes as well: application of presumed stress levels of the peptide chronically (1–2 weeks) onto hippocampal organotypic cultures leads to impoverished dendritic arborization and reduced total dendritic length [68]. Accordingly, preventing CRH-$CRHR_1$ signaling chronically, via pharmacological blockade or genetic knockout of the $CRHR_1$ receptor, leads to exuberant dendritic arborization [68]. These structural changes in CRH-treated or chronically stressed hippocampus, together with structural [17,18,69] and functional [28,70] effects of canonical stress mediators (including glucocorticoids) likely contribute to the well-established deficits in learning and memory [10,11,15]. Whether the effects of CRH and glucocorticoids take place independently, or if there are direct interactions among their signaling pathways within the hippocampus, remains to be determined ([6], see Box 3). However, recent studies using forebrain-specific knockout of $CRHR_1$ suggest that, even in the presence of a functional glucocorticoid system, the absence of $CRHR_1$ attenuates the detrimental effects of chronic stress on dendritic arborization and spatial memory [71].

Taken together, these lines of research illustrate the complex effects of CRH on hippocampal synaptic plasticity and memory function. Although the optimal range of CRH (both the concentration and duration) for facilitating vs. impairing cognitive function remains unclear, the available data suggest that low-level activation of $CRHR_1$ for short

durations can enhance hippocampal function, whereas longer exposure to high levels of CRH may be deleterious. These data may reflect levels of CRH present at hippocampal synapses during acute and long-lasting stress, respectively (see Box 2).

Sculpting of the hippocampus by stress during development: a role for CRH

The developing hippocampus is permanently influenced by chronic stress

The hippocampus is affected by stress throughout the lifespan [6,14,29]. However, whereas the effects of stress on adult hippocampus are generally transient, stress that occurs early in life can permanently alter hippocampus-mediated learning and memory processes [72]. Focusing on chronic and/or severe early-life stress, long-lasting deficits in the Morris watermaze task [73–79], in the relatively stress-free novel object recognition test [73,74,76,78,80,81], and in contextual fear conditioning [81–83] have been found using several different rodent models. Underlying these memory problems are significant and enduring perturbations of hippocampal synaptic plasticity, including selective LTP defects [74,76,84,85]. Notably, although overt impairments of memory and LTP emerged later in life [74,84], more subtle abnormalities in the function and structure of pyramidal neurons could be detected earlier [74,86].

As is the case for the effects of stress experienced in adulthood, early-life stress results in a loss of synaptic plasticity and cognitive function due, at least in part, to a net loss of functional synapses within the hippocampus: chronic early-life stress dramatically reduces dendritic length and branching within CA1 and CA3, in a distribution consistent with the region-selective attenuation of LTP [74,76,87]. The mechanisms for the dendritic abnormalities are unclear: stress could prevent dendritic growth and branching via glucocorticoids [66,69]. Alternatively, dendrites may die back (atrophy), secondary to a loss of functional synapses on the destroyed dendritic spines [67]. In support of this idea, dendritic spines within the adult hippocampus are lost within hours of psychological stress [22,23], and novel mechanisms for these changes are emerging, including glucocorticoid receptor-mediated induction of actin-binding proteins [66]. Upon longer stress durations, this spine loss is eventually followed by a pattern of impoverished dendritic arborization that is similar to the one observed in adult rats experiencing stress early in life [17,18,22,68,76].

How does transient early-life stress impact the hippocampus permanently?

A relatively brief period of neonatal stress may lead to enduring and progressive disturbances of hippocampal structure and function through two broad mechanisms: (1) stress may occur during a sensitive developmental period and thus permanently stunt the maturation and development of the hippocampal network or (2) stress early in life may set in motion changes that lead to progressive injury to hippocampal neurons and eventual disruption of their function. In support of the first possibility, the first 2 postnatal weeks in the rat comprise a crucial age for hippocampal maturation [88]. During this period--comparable to the prenatal (roughly days 0–5) and infancy (second postnatal week) stages of human hippocampus development [88]-- hippocampal commissural/associational (C/A) pathways establish their synaptic connections on CA3 pyramidal cell dendrites [89]. Beyond the 3rd postnatal week, C/A fibers have limited capacity to make synaptic contacts if the original connections are disrupted [90]. Thus, the fact that the structural (dendritic paucity) and functional (LTP) deficits following early-life stress were centered on the C/A fiber system [74] is consistent with a disruption of the maturation of this system. Such disruption might result if, during the critical developmental period, dendritic spines that are the post-synaptic targets of the C/A axons were eliminated by stress, potentially by pathological glucocorticoid or CRH levels within the hippocampus [66,76].

In support of a progressive injury scenario, the cognitive and LTP deficits provoked by early-life stress, as well as dendritic attenuation, appear to emerge later in life and to progress with age [74,76]. Epidemiological studies in humans, though not permitting inferences of causality, are also suggestive of a progressive injury: cognitive problems in individuals with surrogate markers of chronic stress during childhood emerge during middle-age and are a risk-factor for early dementia [91]. Notably, stunted development and progressive injury following early-life stress are not mutually exclusive scenarios: the deficits in hippocampal function over the lifetime may reflect the cumulative effects of both early and continuing processes [7].

Role of CRH in structural and functional effects of early-life stress

Chronic early-life stress produces high levels of systemic glucocorticoids that reach the hippocampus [74], and these hormones can injure dendritic spines [66]. In addition, CRH is released within the hippocampus (see Box 2), and the peptide may be both necessary and sufficient to initiate the changes to hippocampal neurons associated with early-life stress. Application of CRH to organotypic hippocampal slice cultures, (in the absence of glucocorticoids), is sufficient to rapidly reduce spine density [22] and atrophy of dendrites [67] in the same apical dendritic domains that are affected by early-life stress [68,76]. In addition, administration of CRH directly into the brains of infant rats recapitulates the learning and memory problems associated with early-life stress, even when glucocorticoid levels are clamped at physiological levels [92]. Notably, administration of a pharmacological antagonist of $CRHR_1$ during the developmental critical period rescues dendritic structure, LTP and cognitive function of early-stressed rats [76], and mice lacking $CRHR_1$ in the forebrain are resistant to the deleterious effects of chronic early-life stress on hippocampal structure and function [93].

Chronic stress early in life permanently increases CRH expression within the hippocampus [76,94], so that in response to additional, unavoidable stresses throughout life, larger amounts of CRH might be released into the hippocampal neuropil of early-life stressed rats [36,51], thereby contributing to progressive defects of hippocampal structure and function. The mechanisms of the life-long elevation in CRH expression remain unclear, but may involve epigenetic modification of the *Crh* gene [95–98].

Sculpting the aging hippocampus: a role for CRH?

The effects of stress on the aging hippocampus are protean [29], and the role of CRH in the structural and functional changes to the aging hippocampus appears to be dose-dependent. A ‘physiological’ low-level of CRH release might be required for normal cognitive function. In the aging brain, relatively high binding-protein levels sequester the peptide and may impede CRH-$CRHR_1$ signaling [99]. Thus, strategies that aimed to release endogenous CRH from its binding protein, thereby increasing peptide available to bind $CRHR_1$, have improved cognitive outcome in aged rodents [99]. Notably, significant reduction in CRH levels, coupled with augmentation of $CRHR_1$, has been found in patients with Alzheimer’s disease [100,101].

In contrast, subsequent to chronic (or early-life) stress, pathologically high levels of CRH within the hippocampus might be detrimental [74,76]. Stress has been shown to augment tau hyperphosphorylation (a hallmark of neurofibrillary tangles) and β-amyloid levels in transgenic mouse models of Alzheimer’s disease [102,103]. Furthermore, CRH (at high hippocampal levels) may interact with both of these molecules to impair cognitive function [102–104]. Indeed, $CRHR_1$ blockade prior to the stress prevents the subsequent changes in tau phosphorylation [102] and β-amyloid levels [103], as well as the impairments in learning and memory [102]. Even in the absence of stress, high levels of hippocampal CRH are

sufficient to increase both tau phosphorylation [102,104] and β-amyloid levels [103], further confirming a role for CRH in directly regulating these molecules. [102,104][103]Thus, in the aging hippocampus, there may a relative deficit in CRH levels during physiological conditions, but an enhanced sensitivity to the detrimental effects of pathological levels of CRH released during chronic or severe stress [29].

Concluding remarks

The effects of stress on the hippocampus are dynamic and complex, influenced by the duration and context of the stress, as well as by age and gender [5–7,12,13,105]. Because of the prevalence of stress, and the detrimental consequences of chronic stress, the mechanisms by which stress impacts the hippocampus have received significant attention. The intrinsic hippocampal neuro-peptide CRH contributes significantly to these mechanisms, constraining (both temporally and spatially) the neuronal and synaptic populations that are impacted by stress. CRH contributes to stress-adaptive mechanisms that sculpt the hippocampus, designed to improve hippocampal function in acute, threatening circumstances, and perhaps to promote extinction of memories of extremely adverse situations. However, prolongation or hyper-activation of these CRH-mediated mechanisms may lead to maladaptive consequences and long-term cognitive impairments [5–7]. Notably, whereas the current review highlights the important contributions of hippocampal CRH in mediating the effects of stress on the hippocampus, the plethora of structural and functional changes provoked by stress reflects the result of a broad repertoire of stress-activated mediators acting via numerous and likely integrated mechanisms. A key focus for future research is to uncover how CRH interacts with adrenal stress hormones and stress-related neurotransmitters (Box 3). The major challenge will be to examine the interactive, integrated contribution of all of these mediators to the sculpting of the hippocampus by stress.

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Systemic and brain-intrinsic factors mediate the effects of stress on hippocampal neurons

The mechanisms by which stress influences hippocampal neurons involve a broad repertoire of stress mediators and receptors (Figure I) [6]. The perception of stressful signals activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the peripheral release of glucocorticoids from the adrenal gland [5–8,27]. These steroid hormones cross the blood-brain-barrier and reach the hippocampus [30], so that the specificity of their action on neuronal populations is determined by receptor distribution and affinity [11,30]. Both the high-affinity mineralocorticoid (MR) receptor and the lower-affinity glucocorticoid receptor (GR) are expressed in rodent hippocampus, though GR is poorly expressed in stress-sensitive CA3 pyramidal cells [6,11,30]. MR is typically fully occupied under basal conditions, and contributes to neuronal integrity and neurotransmission [6]. In contrast, stress-induced surges of corticosterone saturate the low-affinity GR, enabling a graded response [6]. Interestingly, GR and MR expression are relatively low in primate hippocampus [109], suggesting that additional stress mediators might account for the influence of stress on hippocampus-dependent learning and memory. In addition to corticosteroids, stress induces release of monoamine neurotransmitters and neuropeptides [6,8,110,111]. These molecules influence the hippocampus via their cognate receptors. For example, serotonin [112] and glutamate receptor activation [113] contribute to the effects of stress on hippocampal neuronal structure and LTP, often in concert with glucocorticoids [6]

Physiological and pathological CRH levels in the hippocampus

The actions of CRH on hippocampal structure and function depend on the peptide's concentration at hippocampal synapses. Evidence for tonic release of CRH in the hippocampus is apparent from the abnormal structure of dendrites and dendritic spines that result when CRH receptors are chronically blocked [68], and in mice lacking $CRHR_1$ [22]. Immunocytochemical studies have revealed CRH localization within hippocampal neuropil after stress [50,68], as has been observed previously in the amygdala [54]. CRH is probably relatively stable, because no degrading system has been identified, and a binding protein might sequester or protect the peptide from degradation [114]. In the amygdala and hypothalamus, reported levels of CRH have ranged from 100 – 200 nM [115–117], although microdialysis studies to measure CRH levels in the hippocampus are not yet available.. Therefore, basal and stress levels of CRH at hippocampal synapses remain speculative. Indirect observations suggest that severe stress and network activity (ie. seizures) may lead to hippocampal levels as high as 200nM [118,119].

Outstanding Questions

- What is the relative contribution of CRH signaling to the effects of stress on hippocampus-mediated cognitive functions compared to the other stress mediators (e.g., glucocorticoids?)
- Do CRH and glucocorticoids work independently or in concert to sculpt hippocampal neurons? If so, at what spatial levels (eg. synapse, spine, dendritic branch) and temporal domains (ie. seconds, hours, days) do the interactions take place?
- What is the optimal range of CRH to facilitate synaptic plasticity within the hippocampus and learning/memory functions? Does this range shift during the lifespan?
- Can CRH signaling cascades provide molecular targets to augment and ameliorate the effect of acute and chronic stress on hippocampus-dependent cognitive functions?

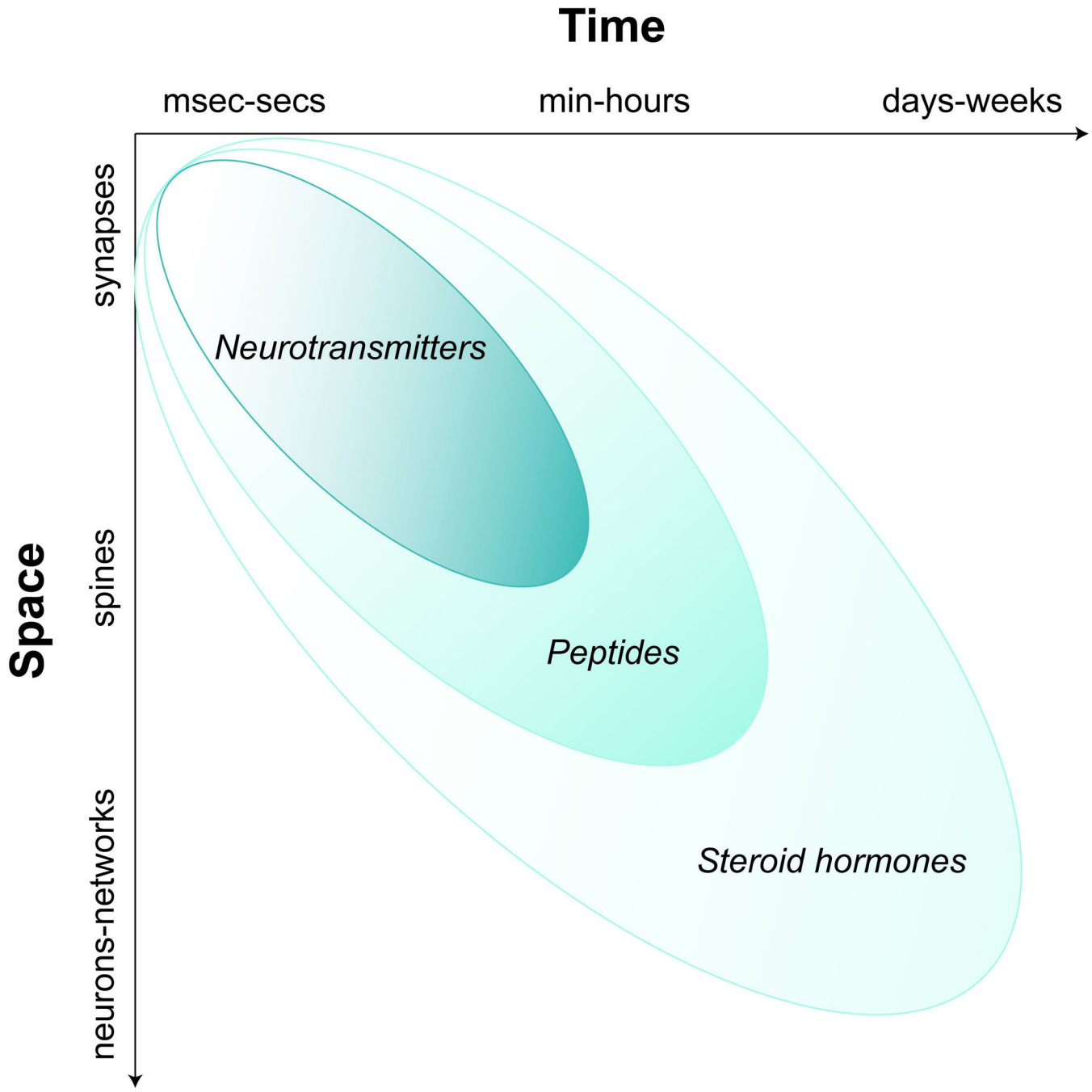


Figure 1. Multiple stress mediators enable precise and coordinated functions in both time and space

Each of the stress mediators generally acts within a given timeframe (horizontal vector). Neurotransmitters can function within milliseconds; steroid hormones employ genomic mechanisms that can persist for months and years; neuropeptides typically act within minutes to hours. Clearly, many exceptions to these general rules exist [6]. The vertical axis delineates spatial domains, which are primarily governed by the location of the released stress-mediator and by receptor distribution. Neurotransmitters generally function at discrete synapses; CRH seems to influence populations of neurons [36,54]; although steroid hormones permeate the entire brain, their actions are constrained by the distribution of

glucocorticoid and mineralocorticoid receptors. The orchestration and integration of the effects of multiple stress mediators are achieved through overlap in these spatial and temporal domains and potentially through direct molecular interactions [6,14].

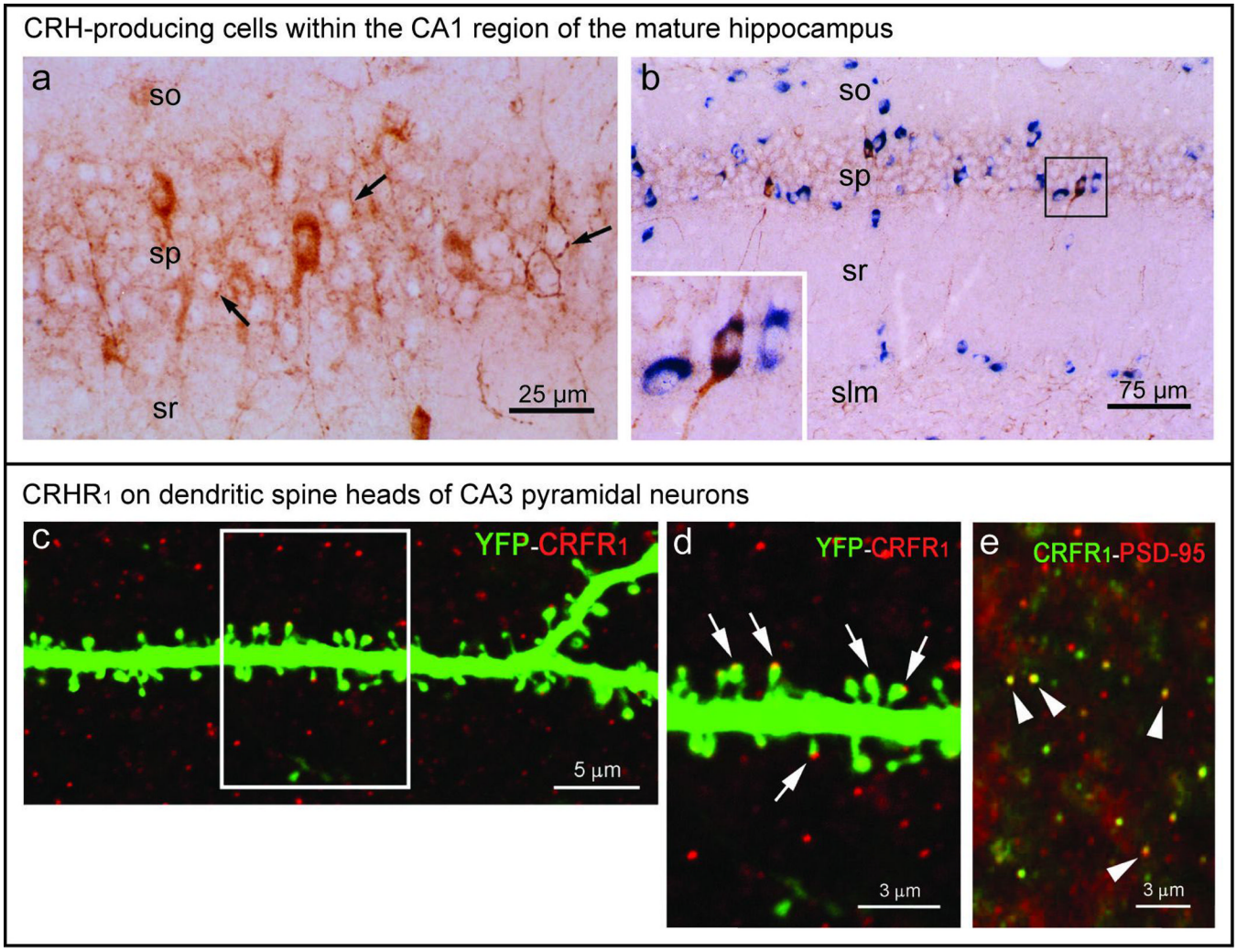


Figure 2. Localization of CRH and $CRHR_1$ within the rodent hippocampus

(*a*) The peptide CRH labeled using immunohistochemistry (brown), is expressed within the pyramidal cell layer of CA1 (and CA3, not shown). (*b*) The majority of CRH-producing cells within adult hippocampus are GABAergic interneurons: co-expression of glutamic acid decarboxylase-65 (GAD_{67}) mRNA (a marker for GABAergic cells) in virtually all CRH neurons is apparent using immunohistochemistry for CRH (brown) combined with *in situ* hybridization for GAD_{67} (blue). (*c*) The CRH receptor $CRHR_1$ (indicated in red) resides on dendritic spine heads (and also on somata, not shown), as shown by confocal microscopy of dendrites from yellow fluorescent protein (YFP)-expressing mice (indicated in green). (*d*) Boxed area in *c*; arrows denote $CRHR_1$ located on spine heads. (*e*) The receptor co-localizes with postsynaptic density protein 95 (PSD-95), a marker for mature spines: confocal microscopic images obtained after dual immunohistochemistry for $CRHR_1$ (green) and PSD-95 (red) illustrate co-labeling of the receptor and spine-head marker (arrowheads). Reproduced, with permission, from [36] (*a, b*) and [50] (*c, d, e*). Abbreviations: so, stratum oriens; sp, stratum pyramidale; sr, stratum radiatum; slm, stratum lacunosum-moleculare.

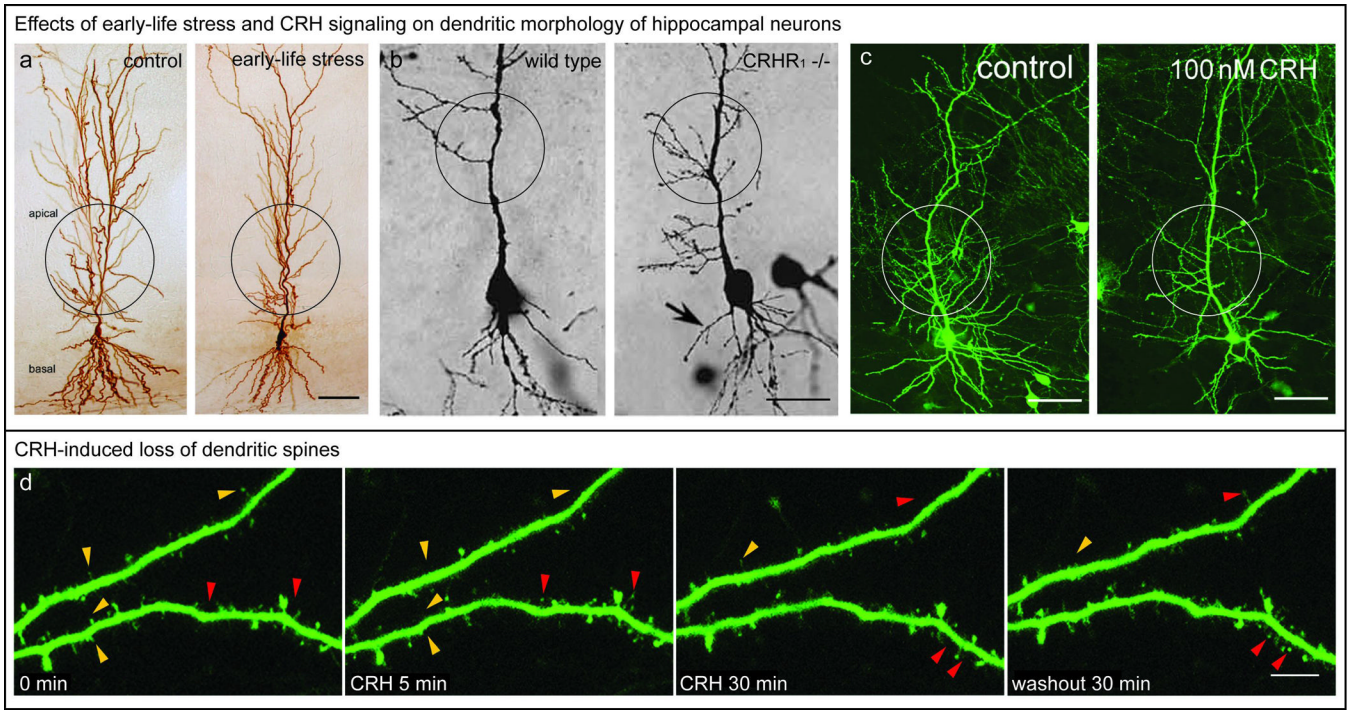
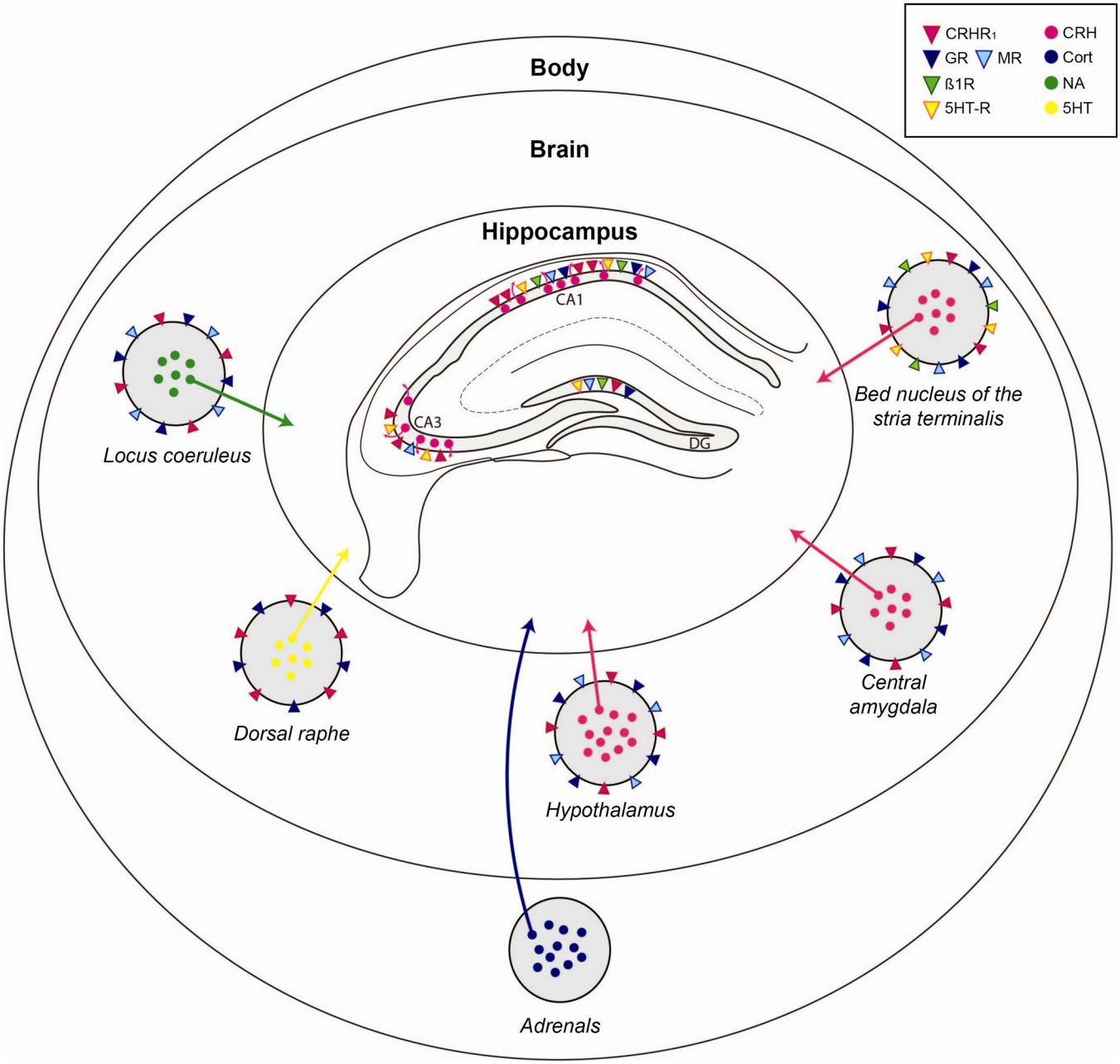


Figure 3. Chronic early-life stress shapes hippocampal dendritic structure: a role for CRH signaling

(*a*) Dendritic impoverishment in pyramidal cells of adult rats that experienced chronic early-life stress (produced using a limited nesting paradigm [74]). Photomicrographs of biocytin-labeled CA1 pyramidal cells illustrate the reductions in total dendritic length and dendritic arborization in the early-stress group (right) compared to controls (left). Scale bar, 80 μm. (*b*) In the absence of $CRHR_1$, the dendritic trees of CA1 (and CA3, not shown) pyramidal neurons are exuberant. Photomicrographs of Golgi-impregnated CA1 pyramidal cells from postnatal day 6–7 mice illustrate increased dendritic length and branching in $CRHR_1$ knockout mice (right), compared to wild type mice (left). Whereas these mice lacked both hippocampal and pituitary CRH receptors, similar findings were also found when growing hippocampi from wild-type and null mice in organotypic slice cultures, suggesting that the dendritic exuberance is a result of a lack of hippocampal CRH signaling [68]. Scale bar, 40 μm. (*c*) CRH application onto hippocampal organotypic slice cultures reduces dendritic complexity. Cultures were prepared from postnatal day 1 yellow fluorescent protein (YFP)-expressing mice and grown either in control media (left) or in the presence of CRH (100 nM; right) for 2 weeks. Scale bar, 70 μm. The circles in *a–c* illustrate the similar distribution of dendritic changes induced by stress and altered CRH signaling. (*d*) A potential mechanism by which CRH may attenuate dendritic length and arborization is through an initial loss of dendritic spines: infusion of CRH (100 nM) onto hippocampal organotypic slice cultures leads to a rapid and reversible loss of spines. High-magnification imaging reveals accelerated spine disappearance that is apparent already by 5 min after the onset of CRH exposure; CRH-induced spine elimination is partially reversed by a 30 min washout. Red arrowheads denote newly formed spines, and the yellow ones show eliminated spines. Scale bar, 6.6 μm. Reproduced, with permission, from [74] (*a*), [68] (*b*), [76] (*c*), and [22] (*d*)



Box 1. Figure I. Distribution of stress mediators impacting the hippocampus

The simplified diagram illustrates the sources of signaling molecules that influence hippocampal neurons during stress. Circles indicate releasable molecules, and triangles indicate their cognate receptors. Abbreviations: DG, dentate gyrus; CRH, corticotropin releasing hormone; $CRHR_1$, CRH receptor type 1; Cort, corticosterone; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; NA, noradrenaline; β1R adrenergic receptor; 5HT, serotonin; 5HT-R, serotonin receptor.

Table 1

Function of CRH-$CRHR_1$ signaling within the hippocampus

CRH application	$CRHR_1$ blockade	$CRHR_1$ knockout
Hippocampal electrophysiology		
Increases excitability	Impairs LTP	Decreases excitability
-*CA1* [40, 41, 49, 58, 65]	-*CA1* [57]	-*CA1* [49]
-*CA3* [40, 41, 49]		-*CA3* [49]
Decreases excitability		Impairs LTP
-*CA1* [106]		-*CA1* [47]
Enhances LTP		
-*CA1* [57]		
Learning and memory function		
Acute administration:		
Improves performance	Prevents stress-induced	Impairs baseline performance
-Passive avoidance [61, 62, 107]	memory impairments	-Spatial memory [52]
-Fear conditioning [57, 58, 63]	-Fear conditioning [57]	
-Spatial memory [64]	-Spatial memory [76]	
	-Object recognition [50, 76]	
Chronic over-expression:		Prevents stress-induced
Impairs performance		memory impairments
-Spatial memory [93, 108]		-Spatial memory [71, 93]
		-Object recognition [71]